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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/993,183	11/14/2001	Alan Gewirtz	43826-9	6995

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EXAMINER	
CHONG, KIMBERLY	
ART UNIT	**PAPER NUMBER**
1635	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/30/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	09/993,183	GEWIRTZ, ALAN	
	Examiner	Art Unit	
	Kimberly Chong	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 January 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,5,7-9,11 and 21-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,5,7-9,11 and 21-38* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *14 November 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application/Amendment/Claims

Applicant's response filed 01/08/2007 has been considered. Rejections and/or objections not reiterated from the previous office action mailed 09/05/2006 are hereby withdrawn. The following rejections and/or objections are either newly applied or are reiterated and are the only rejections and/or objections presently applied to the instant application.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

With entry of the amendment filed on 01/08/2007, claims 1, 2, 5, 7-9, 11, 21-27 and new claims 28-38 are pending in the application.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 30-31 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claims 30-31 are drawn to a method of disrupting expression of a target gene in a human cell comprising exposing the human cell to a dsRNA wherein said dsRNA "has a length less than about 830 bp."

The specification, on page 12, discloses subcloning an 828 bp sequence of c-Kit into an expression vector for use in vitro transcription reactions to produce dsRNA for treating human cells. The claims are drawn to a genus of dsRNA 830 bp or less in length and only one specie of the claimed genus is disclosed, namely an 828 bp sequence. Disclosure of a single species does not represent the entire genus of any dsRNA less than 830 bp. Furthermore, there is no literal support in the instant specification for dsRNA 830 bp in length. If Applicant believes that such support is present in the specification and claimed priority documents, Applicant should point, with particularity, to where such support is to be found.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 26-27 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 recites the limitation "the interfering RNA". There is insufficient antecedent basis for this limitation in the claim. Claim 27 is rejected because it depends on claim 26.

New Claim Rejections - 35 USC § 103

Claims 1, 2, 5, 7-9, 11 and 21-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. (cited on PTO form 892 filed 10/06/2004) as applied to claims 1, 2, 5, 7-9, 11, 21-22 and 24-27 in the 102(e) rejection of record filed 09/05/2006 and in further view of Kreutzer et al. (WO 00/44895, or record), Gewirtz et al (cited on PTO form 892 filed 12/29/2005) and Sharp (cited on PTO form 892 filed 09/05/2006).

The foregoing represents a new rejection necessitated by applicants claim amendments and new claimed filed on 01/08/2007; however Applicants arguments with respect to the above references are addressed below since portions of the arguments are considered relevant to the rejection as newly stated.

The instant claims are drawn to a method for disrupting target gene expression *in vitro* in a human cell comprising providing small interfering RNA sequences which are homologous to a portion of a target gene wherein the target gene is c-Kit, wherein the human cells are particular types of cells, are malignant, that the interfering RNA comprises part of a pharmaceutical composition and that the pharmaceutical composition is used to treat human disease or disorders. Newly amended claims 28-38 are drawn to a method for disrupting expression of a target gene in a human cell comprising selecting a human cell expressing the target and exposing to a dsRNA, measuring the expression of the target gene, wherein the dsRNA is less than 830 bp, wherein the incubating step is about 3 days, wherein the exposing step uses about 150

to 350 ug of dsRNA, wherein the cells are HL-60 or CHP 100 and wherein the dsRNA is KdsRNA.

Fire et al. teach a method for inhibiting expression of a target gene using double stranded RNA to induce RNAi in a cell *in vitro* (Column 26, claim 1) wherein the cell is from an animal (Column 26, claim 6) and the dsRNA has a length of less than about 830 bp (see Table 1). Fire et al. teach that the cell with the target gene may be derived from or contained in any organism (column 8, line 13-14) and that examples of vertebrate animals include mammals and human (column 8, lines 35-37) and that the cell having the target gene may be "immortalized or transformed, or the like" (column 8, lines 52-55) and that "the present invention could be used for treatment or development of treatments for cancers of any type, including solid tumors, sarcomas and leukemias..." (Column 10, lines 26-28). It must be noted that the limitation "selecting a human cell expressing the target gene" is not defined in the specification, so for prior art purposes, this recitation is being interpreted to mean a cell line that contains a target gene and is capable of being treating with a dsRNA and is therefore anticipated by Fire et al. Fire et al. teach target genes that are oncogenes (col. 11). Fire et al. teach that lipid mediated carrier transport can be used to introduce nucleic acids to cells (Column 9, lines 55-60). Fire et al. also teach that inhibition of gene expression refers to the absence (or observable decrease) in the level of protein and/or mRNA product from a target gene as determined by measurement of the target gene or expression from said target gene (Column 6, lines 55-57), thereby indicating disruption of gene function (which is to produce protein). Fire et al. teach that using the methods of their invention,

gene disruptions may be used to discover the function of a target gene and to produce disease models in which the target gene is involved in causing or preventing a pathological condition (col. 5, lines 30-37). Fire et al. disclose, that relative to antisense approaches, their invention has advantages in the stability of the material to be delivered (col. 3, line 20).

Kreutzer et al. teaches a method for disrupting a mammalian target gene in vitro, comprising administering a small double stranded RNA sequence which is homologous to a target gene to induce RNAi, wherein such methods are recited as targeting oncogenes, which is considered to inherently teach targeting cells that reside in a melanoma, leukemia, tumor, or transformed cells population, and wherein said cells are malignant, and wherein the interfering RNA is formulated as part of a pharmaceutical formulation, or wherein the dsRNA targets a human disease or disorder

Fire et al. do not teach the nucleotide sequence of the oncogene c-Kit.

Gewirtz et al. teach the antisense inhibition of c-Kit proto-oncogene expression in human cells and that c-kit antisense oligonucleotides are particularly useful against leukemia and melanoma (see page 15, lines 6-25). Gewirtz et al. disclose that the c-Kit cDNA sequence was known in 1987 and cite Yarden et al. Gewirtz et al. do not specifically teach inhibition in HL-60 cell lines or CHP 100 cell lines. Collin et al. teach HL-60 leukemic cells lines provide a unique and efficient in vitro cell model to study the cellular and molecular events involved in the progression of leukemia (see Abstract page 1233). Likewise Pence et al. teach the CHP 100 neuroblastoma cell line is useful in studying the progression of neuroblastoma in patients.

Sharp is added as a general reference supporting the idea that RNAi is a general mechanism that is likely to be a general mechanism for gene regulation and may be critical for many developmental and antiviral processes.

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the instant invention was made, to substitute an siRNA oligonucleotide in place of the antisense oligonucleotide in a method of inhibiting the expression of the oncogene c-Kit *in vitro* using an antisense inhibitor in human leukemia cells (as taught by Gewirtz et al.), wherein the dsRNA was comprised in pharmaceutical composition (as taught by Fire) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz et al.), because dsRNA can be used to initiate RNA interference *in vitro* by targeting oncogenes in human cells including leukemia (as taught by Fire) and used in vitro to initiate RNA interference in mammalian cells lines (as taught by Kreutzer) and because relative to antisense approaches, dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered (as taught by Fire).

It would have been further obvious to use a HL-60 cell line for the study of leukemia in vitro and further obvious to use CHP 100 to study the cellular events associated with neuroblastoma. Fire et al. does not specifically disclose the optimal time of incubation of said dsRNA with a cell or the optimal concentration of dsRNA used but it would have been obvious to one of skill in the art and a matter of routine optimization to determine the amount of time to expose the dsRNA to the cell to achieve the most efficient gene interference and to determine the optimal workable ranges of a

dsRNA that most efficiently caused gene interference in a cell. MPEP 2144.05 states in part "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation."

One of ordinary skill in the art would have been motivated to practice a method of inhibiting the expression of the oncogene c-Kit *in vitro* in human leukemia cells or melanoma cells (as taught by Gewirtz et al.) using a dsRNA to initiate RNA interference wherein the dsRNA was comprised in pharmaceutical composition (as taught by Fire and Kreutzer) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz et al.) and because relative to antisense approaches, dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered and has advantages of sequence specificity (as taught by Fire et al. and Kreutzer et al).

One of ordinary skill in the art would have expected success in practicing a method of inhibiting the expression of the oncogene c-Kit *in vitro* in human leukemia cells (as taught by Gewirtz et al.) using a dsRNA to initiate RNA interference wherein the dsRNA was comprised in pharmaceutical composition (as taught by Fire and Kreutzer) because antisense inhibition of c-Kit was taught in the prior art as inhibiting the expression of KitR in human leukemia cells (as taught by Gewirtz et al.), because Fire et al. teach that dsRNA can be used to initiate RNA interference in human cells and because relative to antisense approaches, dsRNA used to inhibit gene expression has advantages in the stability of the material to be delivered (as taught by Fire and Kreutzer). Moreover, one would have had a reasonable expectation of success at

initiating RNA interference in human cells given that Kreutzer et al. successfully teach a specific embodiment of RNA interference in a mammalian murine cell line and one of ordinary skill in the art would nevertheless recognize that mice are generally representative of humans. Sharp further supports the fact that RNAi is a general mechanism that is likely to be a general mechanism for gene regulation and may be critical for many developmental and antiviral processes.

Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made.

Response to Applicants Arguments

Re: Claim Rejections - 35 USC § 102

The rejection of claims 1, 2, 5, 7-9, 11, 21-22, and 24-27 under 35 U.S.C. 102(e) as being anticipated by Fire et al. (U.S. Patent 6,506,559, of record) is maintained for the same reasons of record as set forth in the Office Action mailed 5/23/05, 12/29/2005 and 09/05/2006.

At the outset, it must be noted that the above rejection is proper and Fire et al. anticipates claims 1, 2, 5, 7-9, 11, 21-22, and 24-27 because Fire et al. teaches all of the limitations of the instantly claimed elements. It has been noted and previously acknowledged that Fire et al. did not exemplify his invention in human cells but it is not necessary to do so in order to anticipate applicants claimed invention. The enablement requirement for prior art to anticipate under section 102 is different than the enablement requirement required by applicant under section 112. Because applicants have not

shown any manipulative differences or shown any structural differences in the steps used in the instantly disclosed methods as compared to the methods disclosed by Fire et al., applicants position that Fire et al. does not teach or does not enable a skilled artisan to practice each and every limitation of the claimed invention is not convincing. Moreover, as evidenced by Kreutzer et al. above in the new 103 rejection (WO 00/44895, of record), initiation of RNA interference was shown in mammalian murine cells and one of ordinary skill in the art would nevertheless recognize that mice are generally representative of humans in the absence of specific evidence to the contrary. This evidence of RNA interference in mammalian cells coupled with the fact that since the issuance of the Fire et al. patent (Patent No. 6,506,559), which is presumed to be enabling, post-filing art has repeatedly shown that the methods of Fire et al. work in human cells, is additional support that the methods taught by Fire et al. anticipate the instantly claimed invention.

Applicants cite a recently decided Federal Circuit decision (see page 9 of the response filed 01/08/2007, second paragraph) to support their position that in determining whether a prior art reference is enabling, the "...determination is made retrospectively, i.e., by looking back to the filing date of the patent application and determining whether undue experimentation would have been required to make and use the claimed invention at that time." Applicant's contention is that the amount of experimentation required by one of skill in the art to make and use the methods taught by Fire et al. would be amount that is considered undue. In other words, applicant believes there would be more manipulative steps to adapt the methods taught by Fire et

al. to the methods instantly claimed. This is argument is not convincing. As reiterated above, there are no manipulative steps taken by applicant that Fire didn't do that serves to enable the instant invention. As such, the methods taught by Fire et al. anticipate the instantly claimed invention.

Applicants have provided a declaration by Alan Gewirtz and several peer-reviewed references, one of which is by Fire et al., (listed on pages 9-11 of the response) as evidence that the experimentation required to use the methods taught by the Fire et al. (Patent No. 6,506,559) is an amount that is considered undue. This evidence provided by applicant is merely speculation that the methods taught by Fire et al. would not work in mammalian cells and does not in any way indicates undue experimentation would be necessary to practice the methods taught by Fire et al. In fact, this mere speculation has proved to be unfounded given the voluminous post-filing art that has shown the methods of Fire et al. work in human cells. As such, this evidence is not considered sufficient to consider the presumably valid claims of Fire et al. to not be enabled.

Applicants state the facts of the instant application are very similar to those in *In re Goodman* (cited on page 14 of the filed response). Applicants state that despite the fact that Goodman deals with enablement of claims under section 112 and not enablement of an anticipatory reference under section 102, the facts are remarkably similar and therefore because Goodman was found to not be enabling due to the requirement of extensive experimentation to practice the claimed invention, Fire et al. is also not enabled because of the requirement of extensive experimentation to practice

the claimed invention. The decision by the Court in *In re Goodman* is not applicable to the instant application. The enablement requirement for prior art to anticipate under section 102 is different than the enablement requirement required by applicant under section 112 and this fact is made clear by the recent decision by the Federal Circuit in *Impax Labs, Inc. v. Aventis Pharm* (Fed. Cir. 2006) cited by applicant. Here the Federal Court stated "The standard for enablement of a prior art reference for purposes of anticipation under section 102 differs from the enablement standard under 35 U.S.C. §112...While section 112 'provides that he specification must enable one skilled in the art to "use" the invention,'...'section 102 makes no such requirement as to an anticipatory disclosure..."

Therefore, because an issued patent is presumed to be enabled and because applicants have not shown any manipulative differences or shown any structural differences in the steps used in the instantly disclosed methods as compared to the methods disclosed by Fire et al., the methods taught by Fire et al. anticipate the instantly claimed invention.

Re: Claim Rejections - 35 USC § 102

The rejection of record of claims 22 and 24-27 are rejected under 35 U.S.C. 102(b) as being anticipated by Kreutzer et al. (WO 00/44895, or record) is obviated in view of claim amendments filed 01/08/2007.

Claim Rejections - 35 USC § 103

The rejection of record of claims 23-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Fire et al. as applied to claims 1, 2, 5, 7-9, 11, 21-22 above, and further in view of Gewirtz et al (WO 92/19252) Kreutzer et al. (cited above), and Sharp (Genes and Dev. 1999, 13:139-141, cited above) is obviated in view of claim amendments filed 01/08/2007.

No claims are allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kimberly Chong whose telephone number is 571-272-

3111. The examiner can normally be reached Monday thru Thursday between 6 and 3 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Schultz can be reached at 571-272-0763. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public. For more information about the PAIR system, see http://pair-direct.uspto.gov.

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Kimberly Chong
Examiner
Art Unit 1635

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SUPERVISORY PATENT EXAMINER